A within-host dynamic model of *B. pertussis* to support vaccine development

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BACKGROUND

B. pertussis causes a highly contagious respiratory infection known as whooping cough. The development of whole-cell vaccines considerably reduced the incidence of the disease and associated morbidity. Acellular vaccines progressively replaced whole-cell vaccines in the 90s in Europe and the US which, while being highly effective, were associated with non-negligeable side effects. However, the re-emergence of pertussis with recent epidemic episodes raised questions on the efficacy of acellular vaccines for limiting the transmission of the disease. Several parallel hypotheses have been proposed to explain the mechanisms of efficacy of pertussis vaccines. In-host mathematical models, that leverage available data and knowledge of biological mechanisms, are well suited to discriminate between these hypotheses.

In-host mathematical model of *B. pertussis* captures data from **4 immunizations scenarios** and suggest insights on **most impactful factors on efficacy**.

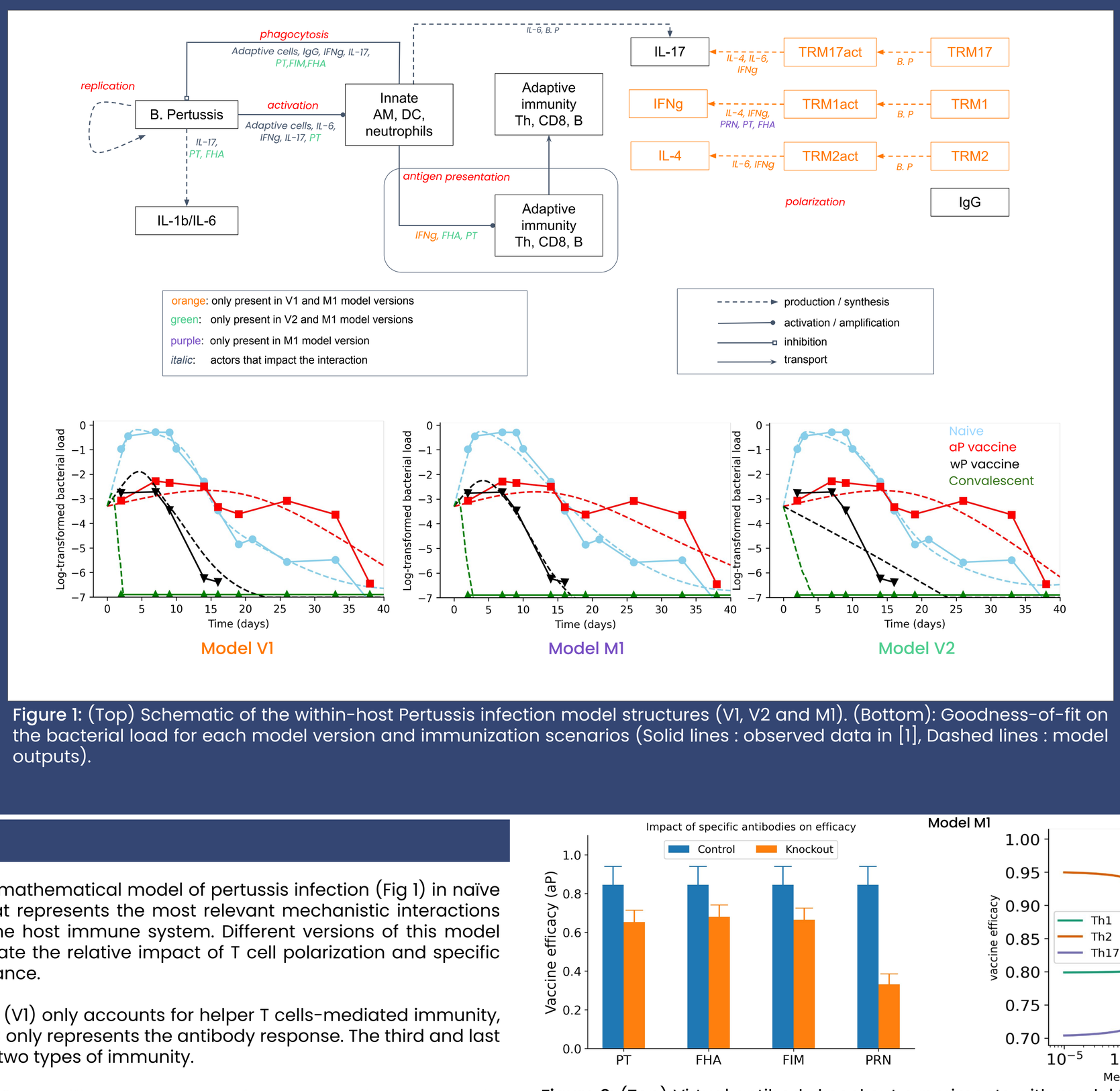

Figure 1: (Top) Schematic of the within-host Pertussis infection model structures (V1, V2 and M1). (Bottom): Goodness-of-fit on the bacterial load for each model version and immunization scenarios (Solid lines : observed data in [1], Dashed lines : model outputs).

METHODS

We developed a within-host mathematical model of pertussis infection (Fig 1) in naïve or immunized individuals that represents the most relevant mechanistic interactions between the bacteria and the host immune system. Different versions of this model were constructed to investigate the relative impact of T cell polarization and specific antibodies on infection clearance.

The first version of the model (V1) only accounts for helper T cells-mediated immunity, while the second version (V2) only represents the antibody response. The third and last version (M1) combines these two types of immunity.

Curation of approximately 250 scientific sources was performed to design the model's equations. Quantitative data from 6 articles were extracted and used to calibrate the model, including bacterial load evolution in challenged baboons with 4 distinct immunization states: primary infection, secondary infection after convalescence, acellular and whole cell vaccination [1].

RESULTS

After calibration, the model versions can reproduce bacterial load evolution in the 4 immunization scenarios (Fig 1). Simulations performed with the model suggest that (Fig 2):

- ➔ the antibody response is probably not the only driver of immune protection.
- ➔ in PRN-containing vaccines, anti-PRN antibodies seemed to be important for the protection conferred by acellular vaccine against colonization, which would explain the emergence of PRN deficient B. pertussis strains.

The model also predicts that the highest increase in vaccine efficacy would be granted by an increase in anti-PRN antibodies (data not shown) or an increase in Th1 or Th17 polarization (Fig 2).

Figure 2: (Top) Virtual antibody knockout experiments with model M1. Impact on vaccine efficacy. (Right) Univariate sensitivity analysis of induced immune factors on vaccine efficacy with model M1 and aP vaccine.

CONCLUSION

- ➔ Such in-host mathematical models could play an important role in the development of new pertussis vaccines by giving insights on the best candidates before their entry into clinical trials.
- ➔ The ability of the models to reproduce results from the literature constitutes evidence of their credibility. However, to further enhance their power of prediction, the models would need to be validated with independent datasets.

REFERENCES

[1] J. M. Warfel, L. I. Zimmerman, T. J. Merkel, Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc. Natl. Acad. Sci. U.S.A. 111 (2013), pp. 787–792.

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